Applicant's Invention

Applicant's invention pertains to methods of treating glycogen storage disease type II (GSD-II) (infantile, juvenile or adult-onset) in an individual. In the methods, a therapeutically effective amount of acid α-glucosidase (GAA) is administered to the individual at a regular interval. The GAA is human acid α-glucosidase (hGAA) produced in Chinese hamster ovary (CHO) cell culture. Production of GAA in CHO cell culture yields a product having glycosylation which allows significant and efficient uptake of hGAA in the desired tissues (heart and muscle). Applicant has successfully treated infants suffering from GSD-II, by administering hGAA to them on a regular basis. The individuals demonstrated improvement of cardiac status, pulmonary function, and neurodevelopment, as well as reduction of glycogen levels in tissue.

Rejections under 35 U.S.C. §102(a)

WO 00/34451

The Examiner rejected Claims 1-5, 8, 16 and 21 as being anticipated by WO 00/34451, stating that WO 00/34451 describes treatment of Pompe's disease by administration of hGAA.

In order for a reference to anticipate claims, the reference must teach every aspect of the claimed invention either explicitly or impliedly (see M.P.E.P. § 2131).

The claims of the invention are drawn to methods of treating glycogen storage disease type II (GSD-II) in an individual, by administering a therapeutically effective amount of hGAA at a regular interval, wherein the hGAA has been produced in Chinese hamster ovary (CHO) cell culture; and to methods of treating cardiomyopathy associated with GSD-II in an individual, by administering a therapeutically effective amount of hGAA at a regular interval, wherein the hGAA has been produced in Chinese hamster ovary (CHO) cell cultures. The terms "treat" and "treatment," as described in the Specification (see, e.g., p. 4, line 20 *et seq.*) refer to amelioration of one or more symptoms associated with the disease, prevention or delay of the onset of one or more symptoms of the disease, and/or lessening of the severity or frequency of one or more symptoms of the disease. Such treatment, for example, can result in improvement of cardiac status (e.g., decrease of left ventricular size and normalization of the ventricular function, or reduction, amelioration or prevention of the progressive cardiomyopathy that is typically found in GSD-II) or of pulmonary function (e.g., increase in crying vital capacity over baseline capacity,

and/or normalization of oxygen desaturation during crying); improvement in neurodevelopment and/or motor skills (e.g., increase in AIMS score); reduction of glycogen levels in tissue of the individual affected by the disease; or any combination of these effects.

WO 00/34451 describes construction of transgenes for production of hGAA in transgenic mice, and sets forth a proposed strategy for enzyme-replacement therapy for patients with Pompe's disease using that hGAA. WO 00/34451 does not teach use of hGAA produced in Chinese hamster ovary (CHO) cell culture for treatment of Pompe's disease, and, in fact, indicates that it is undesirable to utilize enzyme produced in CHO cells, because it is more laborious to produce large amounts needed for clinical therapy by that means (WO 00/34451 at p. 18, lines 20-25). Furthermore, and critically, WO 00/34451 does not teach treatment of disease, as is described in the current Specification and as understood by one of ordinary skill in the art. WO 00/34451 merely describes the potential use of a hGAA for enzyme replacement therapy in individuals with Pompe's disease, but does not indicate whether such therapy actually successfully "treats" the individuals.

In view of these considerations, WO 00/34451 does not teach each and every aspect of the claimed invention: it does not teach use of hGAA produced in CHO cell culture, nor does it teach actual treatment of disease. Therefore, the claimed invention is not anticipated by the teachings of WO 00/34451.

Rejection of Claims under 35 U.S.C. 102(b)

The Examiner set forth several rejections under 35 U.S.C. § 102(b). They are addressed in the order in which they were raised in the Office Action.

de Barsy *et al.* AU2

The Examiner rejected Claims 1-4, 16 and 21 as being anticipated by de Barsy *et al.*, stating that de Barsy *et al.* describe treatment of Pompe's disease by administration of human GAA.

de Barsy *et al.* describe extraction of GAA from human placenta, and administration of a single dose of the GAA to an infant. de Barsy *et al.* report that "no conspicuous morphologic or clinical improvements were noted" in the patient.

de Barsy *et al.* do not describe administration of GAA that has been produced in CHO cell culture. Furthermore, de Barsy *et al.* do not describe administration of GAA at a regular interval: as indicated in the Specification, administration at a "regular interval" indicates that the enzyme is administered periodically, as distinguished from a one-time dose (see, e.g., p. 9, line 11 *et seq.*) In addition, de Barsy *et al.* do not describe "treatment" of disease in an individual as the term is described in the current Specification. In fact, de Barsy *et al.* indicate that there were no physical improvements ("conspicuous morphologic or clinical improvements"); thus, there were no results that one of ordinary skill in the art would consider to be "treatment."

In view of these considerations, de Barsy *et al.* do not teach each and every aspect of the claimed invention: they not teach use of hGAA produced in CHO cell culture, nor do they teach administration of enzyme at a regular interval, nor do they teach actual treatment of disease. Therefore, the claimed invention is not anticipated by the teachings of de Barsy *et al.*

Bijvoet *et al.* AR2

The Examiner rejected Claims 1-4, 8, 16 and 21 as being anticipated by Bijvoet *et al.*, stating that Bijvoet *et al.* describe treatment of Pompe's disease by administration of hGAA.

Bijvoet *et al.* describe production of transgenic recombinant hGAA in mouse milk; administration of a single dose of GAA to GSD-II knockout mice, and a resultant increase of enzyme activity in heart and skeletal muscle samples after two days; and the uptake of the enzyme by cultured human fibroblasts. really?

Bijvoet *et al.* do not describe administration of GAA to an individual. Furthermore, Furthermore, Bijvoet *et al.* do not describe administration of GAA at a regular interval, but rather, use a single dose. In addition, Bijvoet *et al.* do not describe "treatment" of disease in an individual. Neither uptake of enzyme by cultured human fibroblasts, nor increase of enzyme activity in knockout mice administered a single dose of the enzyme, indicates whether administration of the GAA at a regular interval to a patient will, for example, ameliorate one or more symptoms associated with the disease, prevent or delay of the onset of one or more symptoms of the disease, and/or lessen of the severity or frequency of one or more symptoms of the disease.

So what? What does this mean? reads on daily, at last

In view of these considerations, Bijvoet *et al.* do not teach each and every aspect of the claimed invention: they not teach administration of GAA to an individual at a regular interval, or actual treatment of disease. Therefore, the claimed invention is not anticipated by the teachings of Bijvoet *et al.*

Fuller *et al.*

The Examiner rejected Claims 1-4, 9, 10 and 21 as being anticipated by Fuller *et al.*, stating that Fuller *et al.* describe treatment of Pompe's disease by administration of hGAA.

Fuller *et al.* describe preparation of recombinant GAA in CHO cell culture. Fuller *et al.* indicate that the recombinant GAA was taken up in two types of cells from a patient having Pompe's disease: in cultured human skin fibroblasts after exposure to the enzyme for 12 hours, as well as in cultured human muscle cells after exposure to the enzyme for 24 hours. Lysosomal glycogen in the muscle cells was cleared, following addition of recombinant GAA to the culture medium of the cells. Fuller *et al.* do not describe administration of GAA to an individual at a regular interval. Furthermore, Fuller *et al.* do not describe "treatment" of disease in an individual, as that term is described in the current Specification and would be understood by one of ordinary skill in the art. Neither uptake of enzyme by cultured human fibroblasts, nor uptake of enzyme by cultured human muscle cells and subsequent processing of lysosomal glycogen in the muscle cells, both occurring in the short term (e.g., 12 to 24 hours) indicates whether administration of the GAA to a patient at a regular interval will treat the disease (e.g., by ameliorating one or more symptoms associated with the disease, preventing or delaying the onset of one or more symptoms of the disease, and/or lessening the severity or frequency of one or more symptoms of the disease).

In view of these considerations, Fuller *et al.* do not teach each and every aspect of the claimed invention: they not teach administration of human α-glucosidase to an individual at a regular interval, nor do they teach actual treatment of disease. Therefore, the claimed invention is not anticipated by the teachings of Fuller *et al.*

Rejection of Claims under 35 U.S.C. 103

de Barsy *et al.*

The Examiner rejected Claims 1-7, 11-18, and 21 under 35 U.S.C. 102(b) as anticipated by, or, in the alternative, under 35 U.S.C. 103(a) as obvious over, de Barsy *et al.*, stating that "the amounts of enzyme used, the method of administration and intervals at which the enzyme are used are anticipated or in the very least obvious over" de Barsy *et al.*

The rejection of the claims as being anticipated by de Barsy *et al.* is discussed in detail above. As indicated above, de Barsy *et al.* do not describe administration of GAA that has been produced CHO cell culture. While they do state that it is hoped that larger amounts of enzyme will be available in the future (see p. 189), Barsy *et al.* do not teach or suggest any particular amount of enzyme other than the amount they infused (22 "Units", see p. 186, second full paragraph). Furthermore, de Barsy *et al.* do not teach or suggest any regular intervals of administration of the enzyme: they describe only a single administration. Most notably, de Barsy *et al.* do not describe "treatment" of disease in an individual. Thus, de Barsy *et al.* do not teach each and every aspect of the claimed invention, and therefore, the claimed invention is not anticipated by the teachings of de Barsy *et al.*

In order for the claimed invention to have been rendered obvious by the teachings of de Barsy *et al.*, the suggestion or motivation to modify the reference or to combine the reference teachings must be present, and there must be a reasonable expectation of success. (M.P.E.P. 706.02(j)).

One of ordinary skill in the art, given the teachings of de Barsy *et al.*, would not have been motivated to use enzyme produced in CHO cell culture, as there is no teaching or suggestion that enzyme from any source other than placenta as described by de Barsy *et al.* should be used. Furthermore, one of ordinary skill in the art, given the teachings of de Barsy *et al.*, would not have been motivated to try any other dosage regimen or enzyme amount, as there is no teaching or suggestion that alteration of the amount of enzyme or the dosage regimen would yield results different from those described. For example, de Barsy *et al.* do not teach or suggest that administration of enzyme at a regular interval would have a result different from administration of a single dose of enzyme. One of ordinary skill in the art, using the methods of

de Barsy *et al.*, would have at most been motivated only to administer a single dose of the enzyme, and not to administer enzyme at a regular interval.

In fact, one of ordinary skill in the art would not necessarily have been motivated to experiment any further with attempts to treat Pompe disease by administering the enzyme, given the teachings of de Barsy *et al.* that indicated that administration of the enzyme resulted in no physical improvements (no "treatment" occurred). It would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be "treated" by administration of the enzyme; in view of the teachings of de Barsy *et al.*, there would have been no reasonable expectation of success. Applicant has, for the first time, demonstrated successful treatment of disease by administration of the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of de Barsy *et al.*

WO 00/34451

The Examiner rejected Claims 1-4, 8-18, and 21 under 35 U.S.C. 102(a) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over, WO 00/34451, stating that "the amounts of enzyme used, the method of administration and intervals at which the enzyme are used are anticipated or in the very least obvious over" WO 00/34451.

The rejection of the claims as being anticipated by WO 00/34451 is discussed in detail above. As indicated above, WO 00/34451 does not teach treatment of disease; also, WO 00/34451 teaches away from the use of human α-glucosidase produced in CHO cell culture for treatment of Pompe's disease. In view of these considerations, WO 00/34451 does not teach each and every aspect of the claimed invention, and therefore, the claimed invention is not anticipated by the teachings of WO 00/34451.

One of ordinary skill in the art, given the teachings of WO 00/34451, would not have been motivated to use enzyme produced in CHO cell culture, as WO 00/34451 teaches that it is undesirable to utilize enzyme produced in CHO cells, because it is more laborious to produce large amounts needed for clinical therapy by that means. Even assuming *arguendo* that one of ordinary skill in the art attempted to treat Pompe's disease using the methods described in WO 00/34451, one of ordinary skill in the art would not have known whether treatment would be

successful. Given the teachings of WO 00/34451, it would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be "treated" by administration of the enzyme; in view of the teachings of WO 00/34451, there would have been no reasonable expectation of success. Applicant has, for the first time, demonstrated successful treatment of disease by administration of the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of WO 00/34451.

Bijvoet *et al.*

The Examiner rejected Claims 1-7, 11-18, and 21 under 35 U.S.C. 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over, Bijvoet *et al.*, stating that "the amounts of enzyme used, the method of administration and intervals at which the enzyme are used are anticipated or in the very least obvious over" Bijvoet *et al.*

The rejection of the claims as being anticipated by Bijvoet *et al.* is described in detail above. As discussed above, Bijvoet *et al.*, do not describe administration of GAA to an individual at a regular interval, nor do they describe "treatment" of disease in an individual. In view of these considerations, Bijvoet *et al.* do not teach each and every aspect of the claimed invention, and therefore, the claimed invention is not anticipated by the teachings of Bijvoet *et al.*

There is no teaching or suggestion by Bijvoet *et al.* that the enzyme should be administered at a regular interval. One of ordinary skill in the art, using the methods of Bijvoet *et al.*, would have at most been motivated only to administer a single dose of the enzyme, and not to administer enzyme at a regular interval. Furthermore, it would not have been obvious to one of ordinary skill in the art, given the teachings of Bijvoet *et al.*, that the disease could, in fact, be "treated" by administration of the enzyme at a regular interval. Assuming *arguendo* that one of ordinary skill in the art attempted to treat Pompe's disease using the methods described by Bijvoet *et al.*, one of ordinary skill in the art would not have known whether treatment would be successful. The teachings of Bijvoet *et al.* regarding uptake of enzyme by cultured human fibroblasts, and increase of enzyme activity in knockout mice administered a single dose of the enzyme, do not provide a reasonable expectation that administration of the enzyme to a patient at

a regular interval will, in fact, treat the disease. Applicant has, for the first time, demonstrated successful treatment of disease by administration of the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of Bijvoet *et al.*

Fuller *et al.*

The Examiner rejected Claims 1-7, 11-18 and 12 under 35 U.S.C. 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over, Fuller *et al.*, stating that "the amounts of enzyme used, the method of administration and intervals at which the enzyme are used are anticipated or in the very least obvious over" Fuller *et al.*

The rejection of the claims as being anticipated by Fuller *et al.* is described in detail above. As discussed above, Fuller *et al.* do not describe administration of GAA to an individual at a regular interval, nor do they describe "treatment" of disease in an individual. Thus, Fuller *et al.* do not teach each and every aspect of the claimed invention, and the claimed invention is therefore not anticipated by the teachings of Fuller *et al.*

There is no teaching or suggestion by Fuller *et al.* that the enzyme should be administered at a regular interval. One of ordinary skill in the art, using the methods Fuller *et al.*, would have at most been motivated only to administer a single dose of the enzyme, and not to administer enzyme at a regular interval. It would not have been obvious to one of ordinary skill in the art, given the teachings of Fuller *et al.*, that the disease could, in fact, be "treated" by administration of the enzyme. Assuming *arguendo* that one of ordinary skill in the art attempted to treat Pompe's disease using the methods described by Fuller *et al.*, one of ordinary skill in the art would not have known whether treatment would be successful. The teachings of Fuller *et al.* regarding uptake of enzyme by cultured human fibroblasts, and uptake of enzyme by cultured human muscle cells and subsequent processing of lysosomal glycogen in the muscle cells, do not provide a reasonable expectation that administration of the enzyme to a patient at a regular interval will, in fact, treat the disease. Applicant has, for the first time, demonstrated successful treatment of disease by administration of the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of Fuller *et al.*

de Barsy *et al.* in view of Fuller *et al.*

The Examiner rejected Claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over de Barsy *et al.* in view of Fuller *et al.*, stating that it would have been obvious to use the enzyme of Fuller *et al.* in the methods of de Barsy *et al.* and adjust the working conditions accordingly, as well as to use an immunosuppressant or provide instructions with the enzyme.

As described in detail above, de Barsy *et al.* describe extraction of GAA from human placenta, and administration of a single dose of the GAA to an infant. de Barsy *et al.* do not describe administration of GAA that has been produced in CHO cell culture. One of ordinary skill in the art, given the teachings of de Barsy *et al.*, would not have been motivated to look to the teachings of Fuller *et al.* regarding enzyme produced in CHO cell culture, as there is no teaching or suggestion by de Barsy *et al.* that enzyme from any source other than placenta should be used or would have different effects.

Even assuming *arguendo* that the teachings of de Barsy *et al.* were combined with the teachings of Fuller *et al.*, one of ordinary skill in the art would not have obtained the present invention. de Barsy *et al.* do not teach or suggest administration of enzyme at regular intervals, as is claimed in the present invention. One of ordinary skill in the art, using the enzyme of Fuller *et al.* in the methods of de Barsy *et al.*, would have at most been motivated only to administer a single dose of the enzyme, and not to administer enzyme at a regular interval. Furthermore, de Barsy *et al.* do not describe "treatment" of disease in an individual: in fact, they indicate that there were no physical improvements ("conspicuous morphologic or clinical improvements") that one of ordinary skill in the art would consider to be "treatment." Thus, it would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be successfully "treated" by administration of the enzyme of Fuller *et al.* in the methods of de Barsy *et al.* Because it would not have been obvious that treatment would, in fact, result from administration of the enzyme, it would not have been possible for one of ordinary skill in the art to prepare label containing instructions for administration of a composition for treatment of glycogen storage disease type II.

Also, it should be noted that neither de Barsy *et al.*, nor Fuller *et al.*, teach or suggest use of an immunosuppressant in combination with the enzyme, nor do de Barsy *et al.* or Fuller *et al.*

suggest that reactivity of the immune system affected the results in any manner. Thus, it would not have been obvious to one of ordinary skill in the art to administer an immunosuppressant in conjunction with the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of de Barsy *et al.* in combination with Fuller *et al.*

WO 00/34451 in view of Fuller *et al.*

The Examiner rejected Claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over WO 00/34451 in view of Fuller *et al.*, stating that it would have been obvious to use the enzyme of Fuller *et al.* in the methods of WO 00/34451 and adjust the working conditions accordingly, as well as to use an immunosuppressant or provide instructions with the enzyme.

As described in detail above, WO 00/34451 describes construction of transgenes for production of human α-glucosidase in transgenic mice, and sets forth a proposed strategy for enzyme-replacement therapy for patients with Pompe's disease using that human α-glucosidase. However, WO 00/34451 does not teach use of human α-glucosidase produced in CHO cell culture for treatment of Pompe's disease, nor does it teach treatment of disease. One of ordinary skill in the art, given the teachings of WO 00/34451, would not have been motivated to look to the teachings of Fuller *et al.* regarding enzyme produced in CHO cell culture. In fact, WO 00/34451 indicates that it is undesirable to utilize enzyme produced in CHO cells, because it is more laborious to produce large amounts needed for clinical therapy by that means (WO 00/34451 at p. 18, lines 20-25).

Even assuming *arguendo* that the teachings of WO 00/34451 were combined with the teachings of Fuller *et al.*, one of ordinary skill in the art would not have obtained the present invention. WO 00/34451 does not describe "treatment" of disease in an individual; it would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be successfully "treated" by administration of the enzyme of Fuller *et al.* in the methods of WO 00/34451. Because it would not have been obvious that treatment would, in fact, result from administration of the enzyme, it would not have been possible for one of ordinary skill in the art to prepare label containing instructions for administration of a composition for treatment of glycogen storage disease type II.

Also, it should be noted that neither WO 00/34451 nor Fuller *et al.*, teach or suggest use of an immunosuppressant in combination with the enzyme, nor do WO 00/34451 or Fuller *et al.* suggest that reactivity of the immune system affected the results in any manner. Thus, it would not have been obvious to one of ordinary skill in the art to administer an immunosuppressant in conjunction with the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of WO 00/34451 in combination with Fuller *et al.*

Bijvoet *et al.* in view of Fuller *et al.*

The Examiner rejected Claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over Bijvoet *et al.* in view of Fuller *et al.*, stating that it would have been obvious to use the enzyme of Fuller *et al.* in the methods of Bijvoet *et al.* and adjust the working conditions accordingly, as well as to use an immunosuppressant or provide instructions with the enzyme.

As described in detail above, Bijvoet *et al.*, describe production of transgenic recombinant hGAA in mouse milk, administration of the enzyme GSD-II knockout mice, and a resultant increase of enzyme activity in heart and skeletal muscle samples from the mice after two days. They additionally describe and the uptake of the enzyme by cultured human fibroblasts. However, Bijvoet *et al.* do not describe administration of GAA to an individual. One of ordinary skill in the art, given the teachings of Bijvoet *et al.*, would not have been motivated to look to the teachings of Fuller *et al.* regarding enzyme produced in CHO cell culture; in fact, Bijvoet *et al.* teach away from use of enzyme produced in CHO cells, indicating that high production costs associated with use of enzme produced in CHO cells are a significant concern (Bijvoet *et al.*, p. 1820, "Discussion").

they are expensive, but still used.

Even assuming *arguendo* that the teachings of Bijvoet *et al.* were combined with the teachings of Fuller *et al.*, one of ordinary skill in the art would not have obtained the present invention. One of ordinary skill in the art, using the enzyme of Fuller *et al.* in the methods of Bijvoet *et al.*, would have been motivated only to administer a single dose of the enzyme, and not to administer enzyme at a regular interval. Furthermore, Bijvoet *et al.* do not describe "treatment" of disease in an individual; neither uptake of enzyme by cultured human fibroblasts, nor increase of enzyme activity in knockout mice administered a single dose of the enzyme,

indicates whether administration of the GAA to a patient at a regular interval will "treat" the patients. Thus, it would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be successfully "treated" by administration of the enzyme of Fuller *et al.* in the methods of Bijvoet *et al.* Furthermore, because it would not have been obvious that treatment would, in fact, result from administration of the enzyme, it would not have been possible for one of ordinary skill in the art to prepare label containing instructions for administration of a composition for treatment of glycogen storage disease type II.

Also, it should be noted that neither Bijvoet *et al.* nor Fuller *et al.*, teach or suggest use of an immunosuppressant in combination with the enzyme, nor do Bijvoet *et al.* or Fuller *et al.* suggest that reactivity of the immune system affected the results in any manner. Thus, it would not have been obvious to one of ordinary skill in the art to administer an immunosuppressant in conjunction with the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of Bijvoet *et al.* in combination with Fuller *et al.*

Fuller *et al.*

The Examiner rejected Claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over Fuller *et al.*, stating stating that it would have been obvious to use the enzyme of Fuller *et al.* and adjust the working conditions accordingly, as well as to use an immunosuppressant or provide instructions with the enzyme.

As described in detail above, Fuller *et al.* describe preparation of recombinant GAA in CHO cell culture, and indicate that the enzyme was taken up in two types of cells (cultured skin fibroblasts, and cultured muscle cells) from a patient having Pompe's disease. Fuller *et al.* indicate that lysosomal glycogen in the muscle cells was cleared following addition of recombinant GAA to the culture medium of the cells.

Fuller *et al.* do not describe administration of GAA to an individual at a regular interval, nor do they describe "treatment" of disease in an individual. Neither uptake of enzyme by cultured human fibroblasts, nor uptake of enzyme by cultured human muscle cells and subsequent processing of lysosomal glycogen in the muscle cells, indicates whether administration of the GAA to a patient will treat the disease. Given the teachings of Fuller *et al.*,

it would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be successfully "treated" by administration of the enzyme.

Furthermore, because it would not have been obvious that treatment would, in fact, result from administration of the enzyme, it would not have been possible for one of ordinary skill in the art to prepare label containing instructions for administration of a composition for treatment of glycogen storage disease type II.

Also, it should be noted that Fuller *et al.*, do not teach or suggest use of an immunosuppressant in combination with the enzyme, nor do Fuller *et al.* suggest that reactivity of the immune system affected the results in any manner. Thus, it would not have been obvious to one of ordinary skill in the art to administer an immunosuppressant in conjunction with the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of Fuller *et al.*

SUMMARY

As amended, the claims more particularly point out Applicant's invention, specifying that the hGAA has been produced in CHO cell culture. The references used in the rejections under 35 U.S.C. 102 (i.e., WO 00/34451, de Barsy *et al.*, Bijvoet *et al.*, and Fuller *et al.*), fail to teach every aspect of the claimed invention: no single reference teaches treatment of an individual by administration of hGAA at a regular interval, wherein the hGAA is produced in CHO cell culture. Furthermore, these references, when used in the combinations indicated in the rejections under 35 U.S.C. 103, fail to render the invention obvious. The secondary references fail to overcome the deficiencies of the primary references: none of the references, either alone or in combination, teaches or suggests treatment by administration of hGAA at a regular interval, wherein the hGAA is produced in CHO cell culture. Furthermore, given the teachings of the references, one of ordinary skill in the art would not have had a reasonable expectation that disease could, in fact, be successfully "treated" by administration of the hGAA at a regular interval. Thus, the claimed invention would not have been obvious over the cited references.

CONCLUSION

In view of these considerations, the claims are in condition for allowance. Applicant's Attorney requests that the Examiner reconsider and withdraw all objections and rejections.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to call Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to call David E. Brook at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

David E. Brook, R.N. 22592

By for Elizabeth W. Mata

Elizabeth W. Mata
Registration No. 38,236
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: 9/16/02

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method of treating glycogen storage disease type II in an individual, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase at a regular interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell cultures.

8. (Amended) The method of Claim 1, wherein the human acid α-glucosidase is recombinant human acid α-glucosidase that has been produced in chinese hamster ovary cell cultures.

9. (Amended) The method of Claim 1, wherein the human acid α-glucosidase is a precursor of recombinant human acid α-glucosidase that has been produced in chinese hamster ovary cell cultures.

21. (Amended) A method of treating cardiomyopathy associated with glycogen storage disease type II in an individual, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase at a regular interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell culture.

22. (Amended) A pharmaceutical composition comprising human acid α-glucosidase, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell culture, in a container with a label containing instructions for administration of the composition for treatment of glycogen storage disease type II.